REMARKS

Claims 1-33 are pending. Claims 1 and 8 have been amended. Claim 1 has been amended to specify that the formulation also comprises a steroid in suspension and claim 7 has been amended to recite "fluticasone propionate." Support for the amendment to claim 1 is found at page 3, lines 24-26 and in claim 2 as originally filed. Support for the amendment to claim 8 is found at page 9, line 26.

Applicant notes the Examiner's acknowledgement of the priority claims for this application.

The Examiner stated that the August 25, 2008 information disclosure statement did not include a copy of the listed reference (identified as C3 in the Form 1449 accompanying the August 25, 2008 IDS). Applicant encloses a copy of the C3 reference with the present response.

Applicant brings to the Examiner's attention copending application USSN 10/574,302, which discloses related subject matter. This application has published as US2007/021811 and is listed as reference A6 on the modified PTO Form 1449 submitted herewith.

Rejections under 35 U.S.C. § 103(a)

1. Clarke and the Trofast References

Claims 1, 2, 7-10, 13-16, 21, 23-25, 27, 28 and 32 are rejected under 35 U.S.C. § 103(a) as unpatentable over Clarke et al. (US 20020103260) in view of Trofast et al. (WO 92/18110) and Trofast (WO 01/89491). The rejection is traversed to the extent it is applied to the claims as amended.

Claim 1 as amended is directed to a pharmaceutical aerosol formulation for use in a metered dose inhaler (MDI) that includes formoterol fumarate (FF) dihydrate in suspension, a propellant and ethanol, wherein the FF dihydrate has a water content of about 4.8 to 4.28% by weight, and a steroid in suspension. The cited references do not predictably lead one of skill in the art to the claimed invention.

The Examiner contends that the combination of references discloses the general conditions of claim 1. Although the Examiner acknowledges that none of the cited references teach the specific water content of formoterol fumarate, the Examiner contends that "it is not inventive to discover a workable range for the water content discernable by routine experimentation." Office Action at p. 4, para. 2. As to why the skilled person would seek to find such a "workable range" the Examiner contends that the combination of references teaches

"that the stability of formoterol fumarate may be improved by drying the powder prior to mixing it with the other ingredients of an antiasthmatic aerosol composition." Applicant respectfully disagrees with the Examiner's characterization of the cited references and submit that claim 1 is not rendered obvious by their combination.

Contrary to the Examiner's assertion, the combination of cited references does not teach that the stability of FF dihydrate in an aerosol suspension formulation can be improved by drying it prior to mixing with other ingredients. The Examiner relies on Trofast I (referred to by the Examiner as "Trofast et al.") and Trofast II (referred to by the Examiner as "Trofast") to provide this teaching, which is admittedly absent from Clarke. Office Action at p. 3, para. 2 of part 5, to page 4, para. 1.

Importantly, Applicant notes that neither of the Trofast references teaches aerosol formulations at all, much less aerosol suspension formulations of FF dihydrate. Instead, the Trofast references are concerned with dry powder formulations. This is important because the Examiner has not demonstrated why a skilled person desiring to make a stable *aerosol suspension formulation* of FF dihydrate would look to a reference that is concerned with making *dry powder* formulations. The skilled person will appreciate that there are significant differences between dry powder formulations, which are designed for use in a dry powder inhaler ("DPI"), and the aerosol formulations of the invention, which are for use in a metered dose inhaler ("MDI"). For example, rapid particle settling and agglomeration can adversely affect the dose reproducibility of aerosol suspension formulations. So the main technical problems facing aerosol suspension formulations are suspension stability and homogeneity (see Crowder et al., 2001: "An Odyssey in Inhaler Formulation and Design," *Pharma. Tech.* July 2001, pages 99-113, at p. 100, col. 2, para. 2, submitted as reference C4 in the Supplemental Information Disclosure Statement filed with this paper). In contrast, the main technical problems facing dry powder formulations are the powder characteristics, especially particle size and flowability (see Crowder at p. 106, col. 1, para. 3 to col. 2 para. 2).

Even if the skilled person was to look at the Trofast references, their combination does not provide either the specific teaching or a motivation to make an aerosol suspension formulation of FF dihydrate having a water content of <u>about 4.8 to 4.28% by weight</u>. Trofast I is the only reference to address water content and it does not teach that water content is important for the stability of dry powder formulations. Instead, Trofast I teaches that a *conditioning* step, which involves treatment with a solvent, is probably responsible for increasing the stability of the dry powder formulations. See Trofast I at p. 3 lines 20-38, and p. 5, line 37 to p. 6, line 2. ("The conditioning of the substance probably rearrange [sic] the outer layer of the crystals or the

amorphous substance giving a more stable and less hygroscopic product."). Not only does Trofast I fail to teach that a drying step will improve the stability of the formulation, it teaches that the drying step is optional, since it is only performed "if necessary." Trofast I at p. 3 lines 24-26 (reciting step (a) as "reducing, *if necessary*, the residual water from the micronized substance by drying optionally at an elevated temperature and/or vacuum." Emphasis added). Applicant submit that in view of the teaching of Trofast I that a drying step to remove residual water from the micronized substance is optional, the skilled person would not have reasonably expected that reducing the water content of FF dihydrate would increase the stability of FF dihydrate in a dry powder formulation, much less in an aerosol suspension formulation according to claim 1.

The Examiner appears to rely on Trofast II to provide additional motivation to dry FF dihydrate prior to mixing it with other ingredients. Specifically, the Examiner contends that Trofast II teaches that FF dihydrate is prone to degradation when combined with other ingredients having reactive species and that relative humidity influences the stability of the powder. Office Action at p. 4, para. 1. However, instead of teaching that the stability of FF dihydrate can be improved by drying prior to mixing with other ingredients, Trofast II expressly teaches that FF dihydrate alone is highly stable, even at high temperatures and high relative humidities. Trofast II at p. 1, lines 28-29. Trofast II does teach that FF dihydrate is "prone to chemical degradation when in contact with e.g. a reactive species like an aldehyde or under stress conditions e.g. a milling process." Id. at p. 1, line 30 to p. 2 line 2. However, the reference is concerned with stabilizing mixtures of FF dihydrate and carbohydrates. Specifically, Trofast II teaches that FF dihydrate and carbohydrates, such as lactose, while stable individually, tend to form degradation products when combined. Id. at p. 2, lines 12-20. In particular, Trofast II teaches that "[b]y sorption of water a saturated aqueous lactose solution is formed at the surface of the powder mixture" and that "[a] certain amount of formoterol fumarate dissolves in this aqueous solution and is thereby susceptible to degradation." Trofast II concludes by stating that "[t]herefore, the relative humidity, as well as storage temperature, will influence the stability of the powder mixture." Importantly, this latter sentence, which is relied upon by the Examiner for teaching that "relative humidity influences the stability of the powder" refers to a powder *mixture* of FF dihydrate *and a carbohydrate*, such as lactose. Applicant submit that this teaching is not enough to direct the skilled person to dry FF dihydrate prior to mixing with other ingredients in an aerosol suspension formulation which does <u>not</u> contain a carbohydrate. Moreover, Trofast II does not teach a step of drying the FF dihydrate prior to mixing it with the other ingredients in order to stabilize the formulation. See Trofast II at p. 3,

lines 3-11. Thus, Trofast II fails to provide any reason to dry FF dihydrate prior to mixing with other ingredients in a dry powder formulation, much less in an aerosol suspension formulation according to claim 1.

In view of the above Applicant maintains that the skilled person following the teachings of Trofast I and II would have no reasonable expectation of improving the stability of an aerosol suspension formulation of FF dihydrate by drying the FF dihydrate prior to mixing it with other ingredients. Clarke does not remedy the deficiencies of Trofast I and II. In the absence of any such reasonable expectation of success, the combined references cannot render obvious the claimed invention.

In further support of the nonobviousness of Applicant invention, Applicant points to the Declaration of Dr. Rudi Mueller-Walz, Ph.D., submitted herewith. The Declaration discusses Applicant's data demonstrating that formoterol fumarate exists as a mixture of anhydrate and dihydrate forms at water contents of 4.1% and 3.5%. Declaration at para. 5. In contrast, at 4.4% water, the formoterol fumarate is primarily in the dihydrate form. Declaration at para. 4. The data also shows that at 0.7% water, which is the water content just after drying, without exposure to moisture, formoterol fumarate is primarily in the anhydrous form. Thus, merely drying formoterol fumarate would not produce the formoterol fumarate dihydrate. Instead, as Applicant's data shows, the formoterol fumarate dihydrate must be dried and exposed to moisture under controlled conditions to produce a stable product containing primarily the dihydrate form. Absent Applicant's discovery that a water content of about 4.28 to 4.8% is optimal for maintaining the dihydrate form, there was no expectation that drying formoterol fumarate to that specific water content prior to mixing it with other ingredients would produce a more stable formulation. Instead, had the skilled person merely dried FF dihydrate, without allowing it to reabsorb water until it reached a water content of about 4.8 to 4.28% by weight, the FF would have been in an anhydrous form prior to mixing with other ingredients. This would have resulted in an *less* stable formulation as the anhydrous FF adsorbed water during storage of the formulated mixture. Absent the teachings of Applicant's specification, there would have been no reasonable expectation of success in producing a more stable aerosol suspension formulation of FF dihydrate by drying it to a specific water content of about 4.8 to 4.28% by weight prior to mixing it with the other ingredients of the formulation.

In summary, Applicant maintains that the Examiner has failed to establish a *prima facie* case of obviousness because the combination of cited references fails to teach every element of the rejected claims and also fails to provide a reasonable expectation of success in practicing the claimed method. Applicant requests reconsideration and withdrawal of the rejection.

2. Clarke and the Trofast References in View of Kordikowski

Claims 3-6, 17, 21, 22, 26, and 33 are rejected under 35 U.S.C. § 103(a) as unpatentable over Clarke (U.S. 2002/0103260) in view of Trofast I and Trofast II and further in view of Kordikowski (U.S. 2003/0223939). The Examiner cites Kordikowski for its teachings relating to certain dependent claims of claims 1 and 2. Office Action at p. 6, para. 3. However, the teachings of Kordikowski fail to render obvious the subject matter of claims 3-6, 17, 21, 22, 26, and 33 because Kordikowski does not remedy the deficiencies of Clarke, Trofast I, and Trofast II, as discussed above. Accordingly, Applicant requests reconsideration and withdrawal of the rejection.

3. Clarke and the Trofast References in View of Keller

Claims 11, 12, 18, 19, and 29-31 are rejected under 35 U.S.C. § 103(a) as unpatentable over Clarke (U.S. 2002/0103260) in view of Trofast I and Trofast II and further in view of Keller (U.S. 6,475,467). The Examiner cites Keller for its teachings relating to the subject matter of dependent claims 11, 12, 18, 19, and 29-31. Office Action at p. 8, last paragraph. However, the teachings of Keller fail to render obvious the subject matter of claims 3-6, 17, 21, 22, 26, and 33 because Keller does not remedy the deficiencies of Clarke, Trofast I, and Trofast II, as discussed above. Accordingly, Applicant requests reconsideration and withdrawal of the rejection.

4. Davies in view of Clarke

Claim 20 is rejected under 35 U.S.C. § 103(a) as unpatentable over Davies (U.S. 2005/0152846) in view of Clarke (U.S. 2002/0103260). Specifically, the Examiner cites Davies for its teaching that the stability of a formulation comprising formoterol is improved by having less than 500 ppm of water based on total weight of the formulation. Office Action at p. 11, para. 2.

In response, Applicant respectfully submits that the combination of Davies and Clarke does not render claim 20 obvious because the combination fails to provide a reasonable expectation of success in making a suspension formulation of formoterol fumarate dihydrate having a moisture content of from 50 ppm to 800 ppm, as required by claim 20.

Davies describes an aerosol solution formulation to be administered by pMDI, having a suitable shelf-life for pharmaceutical use, comprising formoterol as an active ingredient and having a residual water content of less than 1500 ppm. Davies at para. 27. Example 3 of Davies teaches an inverse linear correlation between formoterol and residual water. Davies at para. 112

and Figure 2. At relative humidity above 1500 ppm formoterol content fell below 90%. Id. Davies also teaches that the presence of water "has to be avoided as much as possible" para. 59. These teachings of Davies regarding solution formulations to not render obvious claim 20, which is directed to a *suspension* formulation because the technical problems between solution and suspension formulations are significantly different. For solution formulations, the main problem is one of stabilizing the active agent in solution. For aerosol formulations, the main problem is the physical stability of the particles, namely their tendency to agglomerate, which is influenced by both moisture content and the crystal structure of the active agents.

To the extent that Davies discusses suspension formulations, it teaches that they are undesirable compared to solution formulations because they "present problems of physical stability" and cannot achieve the ultrafine particle size of solution formulations. Davies at para. 10, 13. Thus, the skilled person following Davies would have no reasonable expectation of improving the stability of an aerosol suspension formulation of FF dihydrate by maintaining the moisture content of the formulation at from 50 ppm to 800 ppm, as required by claim 20.

Clarke does not cure the deficiencies of Davies. Clarke teaches only one example of an aerosol composition of formoterol fumarate dihydrate for a metered dose inhaler yet it teaches 215 dry powder formulations, each of which also contains a carbohydrate (see Clarke, Examples 1-216). There is only one mention of a suspension formulation in the specification of Clarke, at paragraph 11. However, the majority of this paragraph describes an inhalable form comprising the active ingredients "in solution or dispersion." Specifically, there are 4 references to solution or dispersion formulations and only one to a suspension formulation. Thus, the skilled person reading Davies in view of Clarke would have no reason to make a suspension formulation of FF dihyrate, much less one according to claim 20, because Davies teaches that suspension formulations are less stable than solution formulations and Clarke provides many examples of dry powder formulations containing a carbohydrate but only one of an aerosol formulation lacking a carbohydrate.

In summary, Applicant submits that the combination of Davies and Clarke does not provide the reasonable expectation of success required to render the claimed formulation of formoterol fumarate dihydrate <u>in suspension</u> and having a moisture content of from 50 ppm to 800 ppm obvious because Davies teaches that suspension formulations are less desirable then solution formulations and the description of Clarke points toward dry powder formulations rather than aerosol formulations, much less aerosol suspension formulations. Accordingly, Applicant requests reconsideration and withdrawal of the rejection.

Applicant submits that the application is in condition for allowance and request an action for same. A Petition for Extension of Time accompanies this response. Please charge any additional fees that may be due, or credit any overpayment, to Deposit Account No. 50-0311, Reference No. **28069-624N01**.

Respectfully submitted,

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